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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,347	01/25/2002	Ronald M. Burch	200.1079CON2	8306

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DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/056,347	**Applicant(s)** BURCH ET AL.	
	Examiner Jon D. Epperson	**Art Unit** 1639	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 April 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *06 April 2006*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Please see attached sheets.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). 1/25 resubmit on 4/11
13. ☐ Other: _____.

ADVISORY ACTION

Please note: There is a change in Examiner handling prosecution in this case from Padmashri Ponnaluri to Jon Epperson.

Status of the Application

1. The Request for reconsideration filed April 11, 2006 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 38 and 47-52 are currently pending (e.g., see 4/11/06 response, page 4, section A and comments therein). No claims were added, canceled or amended. Therefore, claims 38 and 47-52 are examined on the merits.

IDS

4. The information disclosure statement filed January 25, 2005 (resubmitted on April 11, 2006), fails, in part, to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because one publication cited therein, designated BR, lacks a publication date, a necessary element for consideration. While the other patent and other publications cited therein, and supplied, therewith, have been considered as to the merits, these three publications have not. Applicant is advised that the date of any re-submission of these citations contained in this information disclosure statement or the submission of the missing element – their publication dates – will be the date of submission for purposes of determining compliance with the

requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPE § 609 C(1).

Withdrawn Objections/Rejections

5. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

6. Claims 38 and 47, 48, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. US Pat. No. 4,569,937 (2/86), Engelhardt et al. Inflamm. Res. 44:423-433 (1995), Engelhart Brit. J. Rheumatol. 1996:35(suppl.1): 4-12 and Distel et al. Brit. J. Rheumatol. 1996:35(suppl.1):68-77.

Baker et al. teach pharmaceutical compositions for relieving pain in humans or mammals (e.g. mice, rats etc.) comprising a combination of :

a. a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; mice data in col. 8-10; patent claims), or a pharmaceutically acceptable salt thereof; and

b. ibuprofen (a non-steroidal anti-inflammatory drug or NSAID: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof, in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present claim 47: See col. 2) with oxycodone amounts of about 5 mgs-600mgs (compare to present claim 46).

The Baker reference teaches oral administration (e.g. see present claim 39), which can be coadministered in a "single dosage form" (e.g. see col. 3-8) or sequentially administered (e.g. col. 8-9 ; " ... mice are dosed sequentially..."). The oral dosage forms include "sustained release"

formulations (e.g. tablets, capsules, etc.: see col. 3-4, especially col. 4). The Baker et al. reference teach that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is "unexpectedly enhanced" or synergistic i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components, thereby permitting "reduced dosages of narcotic analgesics" (e.g. oxycodone) AND which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components resulting from high dosages of oxycodone or NSAID"s such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32. Accordingly, Baker would teach the use of therapeutic and subtherapeutic amounts of oxycodone and/or ibuprofen in view of the additive or synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular patient, including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

The Baker analgesic composition differs from that presently claimed in that it fails to teach the substitution of meloxicam for ibuprofen into the Baker compositions.

Engelhardt et al. teach that meloxicam, as compared to other NSAID's (e.g. indomethacin, naproxen etc.) in animal models (e.g. rat):

a. was more efficacious when orally administered in a single dose (e.g. anti-exudative effect; more potent ; more prolonged with a better therapeutic range);

b. had good analgesic effect on inflammatory pain; and

c. had fewer side-effects e.g. inhbited both bradykinin-induced bronchospasm; greater GI tolerance. See e.g. abstract and animal data.

Similarly, Engelhardt teaches that compared to other NSAID's meloxicam has an improved safety profile and good tolerability with high and long-lasting anti-inflammatory and analgesic effects in an animal model (e.g. rats). See abstract and animal data.

Further, the Distel et al. reference teaches that meloxicam is a "preferred NSAID/COX-2 inhibitor" (as compared to other NSAID's e.g. piroxicam/naproxen) which in clinical trials is efficacious in the treatment of arthritic pain patients (e.g. osteo/rheumatoid arthritis) but has shown to be more safe, with reduced side-effects (e.g. dyspepsia, ulcers, reduced hemoglobin, gastritis etc.). See Distel et al. Abstract and disclosed studies.

Accordingly, one of ordinary skill in the art would have been motivated to substitute meloxicam (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Engelhardt et al., Engelhardt and Distel et al. reference teachings that meloxicam is at least equally efficacious, but is safer with less side effects (e.g. as compared to othe NSAID's i.e. ibuprofen).

Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting the NSAID meloxicam for the NSAID in light of the benefits of meloxicam (increased safety/decreased side effect as compared to ibuprofen) as taught by the Engelhardt et al., Engelhardt and Distel et al. references.

Response

7. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "the present claims exclude any other analgesic compound than those recited" and, presumably as a result, this fact distinguishes the presently claimed invention (e.g., see 4/11/06 Response).

[2] Applicants argue, "... the Baker reference teaches narcotic analgesics in combination with ibuprofen, and not in combination with the broad class of NSAIDS [presumably because Baker achieves "unexpected" results with ibuprofen] ... meloxicam would result in a dosage form which is not directed to the principle of operation described in Baker et al. ... [therefore] Baker ... teaches away from substituting ibuprofen with another NSAID (e.g, meloxicam), because of the unexpected synergy that it purports for the combination of ibuprofen" and cite Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH and various passages in Baker et al. in support of this position (e.g., see 4/11/06 Response, pages 5-7).

[3] Applicants argue, "the Examiner is improperly picking and choosing the meloxicam of the Engelhardt et al. Gngelhardt and Distel references with the Oxycodone of Baker et al. to recreate the claim of the present invention" presumably using improper hindsight (e.g., see 4/11/06 Response, page 7). In addition, Applicants' *cite SmithKline Diagnostics, Inc. v. Helena Laboratories Corporation*, 859 F.2d 878, 887 (Fed. Cir. 1988) in support of this position.

This is not found persuasive for the following reasons:

[1] Applicants' arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants recite that their claims are limited to the recited ingredients but don't assert that any of the references require more than these two "essential" ingredients. Thus, Applicants' arguments fail to specifically point out how the claim are patentably distinct from the references.

[2] The Examiner respectfully disagrees. While the Examiner agrees that "a reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be lead in a direction divergent from the path that was taken by the applicant," it should also be noted that "[t]he degree of teaching away will of course depend upon the particular facts [of each individual case]." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994) (citing *United States V. Adams*, 383 U.S. 39, 52, 148 USPQ 478, 484 (1966)). In addition, a reference that "teaches away" does not *per se* preclude a *prima facie* case of obviousness, but rather should be considered as only one factor in determining unobviousness. *Id* at 552. For example, the Court in *In re Gurley* considered a "teaching away" as representing one of several factors in ultimately affirming the board's decision on obviousness. *Id* at 551. Gurley claimed a bendable, epoxy-based printed circuit board. The prior art did acknowledge that epoxy was known for such use, but viewed epoxy containing boards as inferior to polyester-imide-containing boards. Trumpeting this fact, Gurley argued that the prior art "taught away" from his invention. The Court, however, rejected this argument, stating that a "teaching away" represents only one of a

number of factors and held, when properly viewed in this context, that a known or obvious material does not become patentable simply because the art described it as somewhat inferior. *Id.*

Here, the fact that the Baker reference described some of the other NSAIDs as "somewhat inferior" likewise does not preclude a holding that finds the claimed invention obvious. The Baker et al. reference does not state, contrary to Applicants' assertions, that other NSAIDs would fail to provide useful results; nor has Applicants provided any evidence in support of this position. To the contrary, the Baker reference merely states that ibuprofen was unexpectedly better than the other NSAIDs tested, which implies that the other NSAIDs also functioned to improve analgesic activity albeit to a lesser extent. Consequently, Applicants' *per se* rule that all "somewhat inferior" embodiments would necessarily "change the principle of operation" or "discourage others from the path set forth in the reference" is not consistent with *In re Gurley*. In addition, the Examiner notes, "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989)" (e.g., see MPEP § 2123).

Finally, this position is consistent with *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). *In re Fine* involved a system for measuring minute quantities of nitrogen presumably for the detection of drugs and explosives. The claims were rejected as being obvious over Eads in view Warnick. Eads disclosed a method for separating and identifying sulfur compounds. Warnick disclosed a process for detecting pollutants in the atmosphere by measuring the level of nitric oxide. The PTO held that it would have been *prima facie* obvious to substitute the nitric oxide detector of Warnick for the sulfur dioxide detector of Eads. On appeal, the Federal Circuit

reversed noting that Eads deliberately sought to avoid the use of nitrogen because the sulfur detector was adversely affected by substantial quantities of nitrogen. Thus, according to the CAFC, "instead of suggesting that the system be used to detect nitrogen compounds, Eads deliberately seeks to avoid them; it warns against rather than teaches Fine's invention." See *Id.* at 1599. Thus, *In re Fine* provides an example of a "teaching away" by disclosing that the presence of a claimed element, nitrogen, is undesirable. No such "teaching away" exists in the present case. That is, the Baker reference never states that the addition of other NSAIDs or the substitution of other NSAIDs for ibuprofen would somehow destroy "adversely affect" or "destroy" the therapeutic composition. At most, the Baker reference merely implies that these other therapeutics wouldn't "help" as much.

Therefore, in view of the above, the evidence of obviousness, on balance, outweighs the evidence of nonobviousness proffered by the appellants. That is, preferred disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. See MPEP § 2123.

[3] In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Here, the Engelhardt et al. reference, not Applicant's specification, explicitly states that Meloxicam compares favorably to all other NSAIDs, which

would encompass by extrapolation ibuprofen (e.g., see Engelhardt et al., page 430, column 2, Discussion section, "The data reported here show that meloxicam differs from classical NSAIDs with respect to its ... analgesic ... properties. Most significantly, the gastro-intestinal tolerance in relation to the anti-inflammatory potency of meloxicam is much more favourable than that of all other NSAIDs tested"; see also page 431, column 2, second to last full paragraph, "Like other NSAIDs, meloxicam shows a good analgesic effect on inflammatory pain ... Meloxicam had the most persistent effects of all the compounds investigated"). Therefore, the prior art, not Applicants' specification, suggests the claimed composition.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

8. Claim 38 and 47-52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. '937, Engelhardt et al., Engelhart , and Distel et al as applied to 38 and 47, 48, 51 and 52 claims above, and further in view of Oshlack et al. US Pat. No. 5,472,712 (12/95) or Oshlack et al. US Pat. No. 6,294,195 (9/01: effectively filed 10/93 or earlier).

The substance of the above obviousness rejection is hereby incorporated by reference in its entirety.

Although the Baker reference teaches oral dosage forms which include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4) utilizing "sustained release carriers", the Baker reference fails to explicitly teach "a sustained release carrier which provides a sustained release of the oxcodone and/or ... salt thereof".

However, the use of sustained release dosage forms for opioid analgesics, including oxycodone which utilize sustained release carriers employing beads which are coated with the

opioid drug or which include substrate layers which include the drugs is known in the art to effectuate delayed release of extended duration. E.g. see Oslack et al. and Oshlack patent references.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize sustained release carriers for oxycodone including beads/layers as taught by the Oshlack and Oshlack et al. patents for use in the Baker compositions since Baker specifically teaches using "sustained release formulations" and further in view of the advantages of utilizing the Oshlack patent sustained release carriers including delayed drug release of extended duration.

Response

9. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "Oshlack references do not cure the deficiencies of the Baker reference ... set forth above" (e.g., see 4/11/06 Response, page 8, last paragraph).

This is not found persuasive for the following reasons:

The Examiner contends that to the extent that Applicants are simply repeating their previous arguments, those issues were adequately addressed in the above sections, which are incorporated in their entirety herein by reference.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Persuasive for the following reasons. Please note that the above rejection has been modified

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 30, 2006

JON EPPERSON, PH.D.
PATENT EXAMINER